1,003,292

PATENT SPECIFICATION

NO DRAWINGS

1,003,292

Date of Application and filing Complete Specification: Nov. 13, 1961.
No. 40463/61.
Application made in Switzerland (No. 13757) on Dec. 8, 1960.
Application made in Switzerland (No. 10835) on Sept. 19, 1961.
Complete Specification Published: Sept. 2, 1965.

Index at acceptance:—C2 C(2A3, 2A5, 2A14, 2B3A4, 2B3F, 2B3G1, 2B3G4, 2B3G7, 2C4, 2C6F, 2C7A2, 2R17, 3A13A3A4, 3A13A3B3, 3A13A3C, 3A13A3F3, 3A14A3C, 3A14A8C, 3C5A4, 3C5C2, 3C5E2, B4A1, B4A2, B4A4, B4D, B4E, B4J, B4M)

Int. Cl.:—C 07 d

The inventors of this invention in the sense of being the devisers thereof within the meaning of Section 16 of the Patents Act 1949, are:—ERNST JUCKER, Steinweg, Ettingen/Baselland Switzerland and ANTON EBNÖTHER, Klingnaustrasse 6, Basel, Switzerland, both Swiss citizens.

COMPLETE SPECIFICATION

Improvements in or relating to 4-Azathiaxanthene Derivatives

SPECIFICATION NO. 1,003,292

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of WESTMINSTER BANK LIMITED, of 41, Lothbury, London, E.C.2., a British Company.

THE PATENT OFFICE D 42120/20

ERRATA

SPECIFICATION No. 1,003,292
Amendment No. 1

Page 1, line 50, *for* "alky" *read* "alkyl"
Page 4, line 21, *for* "3" *read* "9"
Page 4, line 93, *for* "piperidene-" *read* "piperidylidene-"
Page 4, line 127, *for* "hair" *read* "hairs"
Page 7, line 52, *for* "fumarate" *read* "fumarates"

THE PATENT OFFICE
23rd September 1965

R_2, R_3, R_6 and R_7 signifies a hydrogen atom or methyl or ethyl radical and each of R_4 and R_5 signifies an alkyl radical con-

their acid addition salts, characterised in that water is split off from a 9 - hydroxy - 4 - aza - thiaxanthene derivative of general formula IV,

[*Price 4s. 6d.*]

A04

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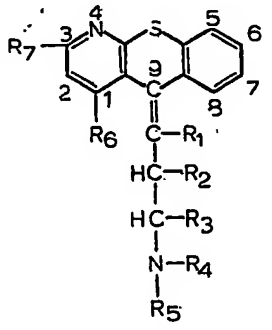
COMPLETE SPECIFICATION

Improvements in or relating to 4-Azathiaxanthene Derivatives

We, SANDOZ PATENTS LIMITED, of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new 4-aza - thiaxanthene derivatives and to a process for their production.

The present invention provides 4 - aza - thiaxanthene derivatives of general formula I,



I

in which

R_1 signifies a hydrogen atom,

each of

R_2, R_3, R_6 and R_7 signifies a hydrogen atom or methyl or ethyl radical and

each of

R_4 and R_5 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive or

R_4 and R_5 together signify an alkylene radical containing 4 or 5 carbon atoms, which alkylene radical may have interposed an oxygen atom or a nitrogen atom substituted with an alkyl radical containing from 1 to 4 carbon atoms inclusive, with the proviso that, when R_5 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive, two of the symbols, R_1, R_2 and R_3 may each signify a hydrogen atom and the third together with R_4 a straight chain alkylene radical containing from 2 to 4 carbon atoms inclusive, and the further proviso that when the 9 - substituent is heterocyclic the ring of which it consists or which forms part of it must be a 5 or 6 membered one, their acid addition salts and pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, a compound I and/or an acid addition salt thereof.

Preferably, when R_4 together with R_1, R_2 or R_3 form a heterocyclic ring with the nitrogen atom adjacent to R_4, said heterocyclic ring is an alkyl (C_1-C_4) - pyrrolidyl or alkyl (C_1-C_4) - piperidyl radical. Preferably also, when R_4 and R_5 together with the nitrogen atom adjacent to them form a heterocyclic ring, said ring is a pyrrolidyl, piperidyl, alky(C_1-C_4)piperazyl or morpholyl radical.

The present invention also provides a process for the production of compounds I and their acid addition salts, characterised in that water is split off from a 9 - hydroxy - 4 - aza - thiaxanthene derivative of general formula IV,

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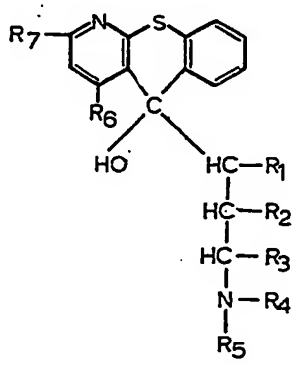
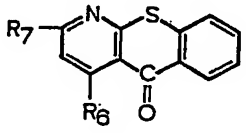


IV

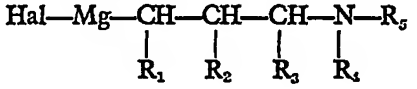
in which R_1 to R_7 have the above significance, and, when an acid addition salt is desired, salification is effected with an organic or inorganic acid. The resulting compound I may be separated into its stereoisomeric forms in accordance with a known method.

Compound IV may be formed by hydrolysing a complex formed by condensing a 4-azathiaxanthone of general formula II,



II

in which R_6 and R_7 have the above significance, with an organometallic compound of general formula III,



III

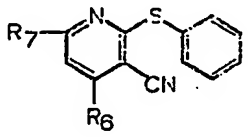
in which R_1 to R_5 have the above significance, Hal signifies a chlorine, bromine or iodine atom.

The process in accordance with the invention may, for example, be effected as follows:—A solution of a Grignard reagent (magnesium or a magnesium alloy, e.g. copper magnesium alloy may be used for preparing it) of the formula III above is produced in manner known *per se*. A compound of the general formula II above is added to the said Grignard reagent solution and the resulting mixture is heated so as to complete the reaction. The reaction product resulting in this manner is then hydrolysed in the cold with an aqueous ammonium chloride solution and extraction is effected by means of an inert organic solvent which is immiscible with water, preferably chloroform, methylene chloride or diethyl ether. In order to isolate the resulting compound IV above, distillation or crystallisation may be effected and conversion into acid addition salts may likewise be effected; however, further working up may be effected without purification. Dehydration is effected by heating the compound IV dissolved, for example, in glacial acetic acid with a dehydrating agent (for example concentrated hydrochloric acid, concentrated sulphuric acid, acetic anhydride, phosphorus oxychloride, thionyl chloride or zinc chloride). The end product may be isolated and purified using a known method; as already indicated above, separation into the individual stereoisomers and/or conversion into an acid addition salt, for example by reaction with hydrochloric, hydrobromic, sulphuric, citric, oxalic, tartaric, succinic, maleic, acetic, benzoic, hexahydrobenzoic, methanesulphonic or fumaric acid, may be effected.

Compounds I are basic compounds which at room temperature are either oily or crystalline.

They may be used as intermediate compounds in the production of pharmaceuticals or have themselves pharmaceutical properties. The compounds I, especially the exemplified ones, have a histamine - inhibiting, narcosis potentiating and sedative effect the extent of which depends on the nature of the substituents. The exemplified compounds I with a piperidylidene substitutent have a particularly strong histamine inhibiting effect and additionally have a serotonin antagonistic effect; the remaining exemplified compounds I furthermore have an adrenolytic effect.

Compounds II, in which R_6 and/or R_7 signify a methyl or ethyl radical are new and are produced in the following manner:—A 5 - cyano - 6 - halogeno - pyridine substituted in the 2- and/or 4-position with a methyl or ethyl radical in which "halogeno" signifies a chlorine or bromine atom, is condensed at an elevated temperature with an alkali metal thiophenolate, the resulting 5 - cyano - 6 - phenyl - mercapto - pyridine derivative of general formula V,



V

in which R_6 and R_7 have the above significance, is hydrolysed and subsequently cyclised.

In the following non-limitative Examples all temperatures are stated in degrees Centigrade and are corrected. The "10% ammonium chloride solution" used in said Examples is expressed by weight.

EXAMPLE 1

a) 9 - (3^1 - dimethylamino - propyl) - 4 - aza - thiaxanthydrol

2.5 g of an activated copper - magnesium alloy (87% magnesium, 13% copper, according to Gilman) are covered with a layer of 15 cc of tetrahydrofuran and 0.3 cc of ethylene bromide are added. Upon commencement of the reaction a solution of 11.3 g of dimethylaminopropyl chloride in 20 cc of ether are added dropwise and the mixture then heated at reflux for 3 hours. A total of 5 g of 4-aza-thiaxanthone (melting point 234°) are then added portionwise to the mixture which has been cooled to 30° and subsequently 10 cc of tetrahydrofuran are added. To complete the reaction the mixture is heated at reflux for a further hour. The cooled reaction mixture is then poured into 250 cc of a 10% ammonium chloride solution. The undissolved metal residues are filtered off and the filtrate shaken with chloroform. After drying of the chloroform extract over potassium carbonate the solvent is evaporated and the residue rubbed with petroleum ether, oil contaminated crystals precipitating. The solvent is decanted and the solute crystallised from acetone and ethyl acetate. 9 - (3^1 - dimethylaminopropyl)-4 - aza - thiaxanthydrol melts at 128—129°.

b) 9 - (3^1 - dimethylamino - propylidene) - 4-aza - thiaxanthene.

45 g of the resulting 9 - (3^1 - dimethyl - aminopropyl) - 4 - aza - thiaxanthydrol are heated at reflux for one hour in 45 cc of concentrated hydrochloric acid. The reaction mixture is then evaporated in a vacuum, the residue dissolved in water, the aqueous solution made alkaline with sodium hydroxide and the mixture shaken with chloroform. After drying of the chloroform extract over potassium carbonate and evaporation of the solvent, the residue is taken up in hexane. Undissolved flakes are filtered off and the solution again evaporated. The oily residue is dissolved in methanol, the solution brought to a pH value of 5.8 with hydrobromic acid and evaporated in a vacuum. The residue, which is mainly crystalline, is recrystallised from ethanol, the *isomer A* of 9 - (3^1 - dimethylamino - propylidene) - 4 - aza - thiaxanthene separating as the hydrobromide. After crystallisation from ethanol it melts at 223—225°.

The *isomer B* of 9 - (3^1 - dimethylaminopropylidene) - 4 - aza - thiaxanthene is isolated as follows:—The ethanolic mother liquor obtained after separation of the isomer A is evaporated. The residue is then shaken with chloroform and a dilute sodium hydroxide solution, the chloroform phase dried over potassium carbonate and evaporated. The remaining oil is dissolved in ethanol and the calculated quantity of fumaric acid added. After addition of ether the isomer B of 9 - (3^1 - dimethylaminopropylidene) - 4 - aza - thiaxanthene crystallises as the acid fumarate. After recrystallising twice from isopropanol the salt melts at 151—153° decomposition).

EXAMPLE 2

a) 9 - [1^1 - methyl - piperidyl - (4^1)] - 4 - aza - thiaxanthydrol

3 g of an activated copper - magnesium alloy (87% magnesium, 13% copper, according to Gilman) are covered with a layer of 15 cc of tetrahydrofuran and 0.4 cc of ethylene bromide are added. Upon commencement of the reaction a solution of 15 g of 1 - methyl-4 - chloro - piperidine in 30 cc of tetrahydrofuran are added dropwise and subsequently heating is effected at reflux for 2 hours. 8 g of 4 - aza - thiaxanthone (melting point 234°) are then added portionwise to the mixture cooled to 40°. To complete the reaction, the mixture is heated at reflux for a further hour. The cooled reaction mixture is then poured into 300 cc of a 10% ammonium chloride solution. The undissolved metal residues are filtered off and the filtrate shaken with chloroform. After drying of the chloroform extract over potassium carbonate the solvent is evaporated and the oily residue boiled with ether. The mixture is decanted from the resins and the solution treated with animal charcoal. Upon cooling of the filtrate oil contaminated crystals separate very slowly. They are recrystallised twice from acetone. 9 - [1^1 - methyl-piperidyl - (4^1)] - 4 - aza - thiaxanthydrol melts at 174—175°.

b) 9 - [1^1 - methyl - piperidylidene - (4^1)]-4 - aza - thiaxanthene

4.5 g of the resulting 9 - [1^1 - methyl - piperidyl - (4^1)] - 4 - aza - thiaxanthydrol are heated to 140° for 25 minutes in 45 cc of 85% by volume sulphuric acid. The reaction mixture is subsequently poured into ice water, the solution made alkaline with potassium hydroxide and the aqueous alkaline solution extracted with methylene chloride. After drying of the methylene chloride extract over potassium carbonate the solvent is evaporated and the remaining 9 - [1^1 - methyl - piperidylidene - (4^1)] - 4 - aza - thiaxanthene recrystallised twice from acetone. Melting point 166—167°.

EXAMPLE 3

a) 3 - methyl - 9 - (3^1 - dimethylamino - propyl) - 4 - aza - thiaxanthydrol.

6 g of an activated copper - magnesium alloy (87% magnesium, 13% copper, according to Gilman) are covered with a layer of 20 cc of ether and 20 cc of tetrahydrofuran and 0.5 cc of ethylene bromide are added. Upon commencement of the reaction a solution of 27 g of dimethylamino - propyl chloride in 30 cc of ether are added dropwise during the course of 20 minutes and the mixture then heated at reflux for a further 2 hours. A total of 12 g of 3 - methyl - 4 - aza - thiaxanthone

(melting point 150—151°) are then added portionwise to the mixture which has been cooled to 30°. To complete the reaction the mixture is heated at reflux for a further hour. The cooled reaction mixture is then poured into 600 cc of a 10% ammonium chloride solution. The undissolved metal residues are filtered off and the filtrate extracted a number of times with chloroform. After drying of the combined chloroform extracts over potassium carbonate the solvent is evaporated, the residue boiled with hexane, the solution decanted from the undissolved resins and treated with animal charcoal. Upon cooling of the filtrate the 3 - methyl - 9 (3^1 - dimethylamino - propyl) - 4 - aza - thiaxanthydrol crystallises. After crystallisation from acetone it melts at 145—146.5°.

b) 3 - methyl - 9 - (3^1 - dimethylamino - propylidene) - 4 - aza - thiaxanthene.

11 g of 3 - methyl - 3 - (3^1 - dimethylamino - propyl) - 4 - aza - thiaxanthydrol are heated at reflux for one hour in 100 cc of concentrated hydrochloric acid. The solution is then evaporated in a vacuum, the residue dissolved in water, the mixture made alkaline with sodium hydroxide and the solution extracted three times with chloroform. After drying of the combined chloroform extracts over potassium carbonate and evaporation of the solvent, the residue is taken up in hexane. The filtered solution is then further evaporated, the remaining oil dissolved in ethanol, the solution brought to a pH value of 5.8 with hydrobromic acid and evaporated to dryness in a vacuum. The isomer *A* of 3-methyl-9-(3^1-dimethylamino - propylidene) - 4 - aza - thiaxanthene crystallises as the hydrobromide from isopropanol/ether. The salt is recrystallised twice from ethanol. Melting point 188—189°.

The *isomer B* of 3 - methyl - 9 - (3^1-dimethylaminopropylidene) - 4 - aza - thiaxanthene is isolated as follows:—The isopropanol/ethereal mother liquor obtained after the separation of isomer A is evaporated. The residue is then shaken with chloroform and dilute sodium hydroxide, the chloroform phase dried over potassium carbonate and evaporated. The remaining oil is dissolved in a fourfold quantity of ethanol, the calculated quantity of fumaric acid added and the mixture heated until complete dissolution has taken place. The isomer B of 3 - methyl - 9 - (3^1-dimethylamino - propylidene) - 4 - aza - thiaxanthene crystallises in the cold as the acid fumarate. The salt is recrystallised three times from ethanol. Melting point 183—185°.

The 3 - methyl - 4 - aza - thiaxanthone used as a starting material is prepared as follows:—76.2 g of 2 - methyl - 5 - cyano-6 - chloro - pyridine and 72 g of dry sodium thiophenolate are heated at reflux in 600 cc of dioxane for 20 hours. The separated salt is removed from the cooled reaction mixture by filtration and the filtrate evaporated in a vacuum. The residue is taken up in methylene chloride, the solution washed twice with water, dried over magnesium sulphate and evaporated. The residue, 2 - methyl - 5 - cyano - 6-phenylmercapto - pyridine, is subsequently recrystallised from methanol. Melting point 80—81°.

90 g of the resulting compound are heated to 140° in 800 cc of concentrated sulphuric acid/water (volume 1:1) for 16 hours. The mixture is then poured into ice water and brought to a pH value of 4 with sodium hydroxide, the 2 - methyl - 5 - carboxy - 6 - phenylmercapto - pyridine separating. The compound melts at 180—181°.

25 g of 2 - methyl - 5 - carboxy - 6 - phenylmercaptopyridine are heated with 200 g of polyphosphoric acid to 120° for one hour and then to 150° for 15 minutes. 800 cc of ice water are then added to the cold reaction mixture whilst stirring well. The precipitated substance is filtered off, suspended in a 1N sodium hydroxide solution, again filtered off, washed well with water and recrystallised from methanol. 3 - methyl - 4 - aza - thiaxanthone melts at 150—151°.

Example 4

3 - methyl - 9 - [1^1 - methyl - piperidene-(4^1)] - 4 - aza - thiaxanthene

In a manner analogous to that described in Example 2 a Grignard compound is produced from 2.7 g of a copper - magnesium alloy and 13.4 g of 1 - methyl - 4 - chloro - piperidine in 40 cc of tetrahydrofuran. 6 g of 3 - methyl-4 - aza - thiaxanthone (melting point 150—151°) are then added portionwise to the Grignard compound at approximately 30° and the mixture stirred for one hour at room temperature. The reaction mixture is subsequently poured into 300 cc of a 10% ammonium chloride solution, the undissolved metal residues are filtered off and the filtrate extracted with chloroform. After drying of the chloroform extract over potassium carbonate and evaporation of the solvent, the residue is boiled with ether. The resins are filtered off and the solution again evaporated. The yellow, viscous residue, 3 - methyl - 9 - [1^1 - methyl-piperidyl - (4^1)] - 4 - aza - thiaxanthydrol, is directly processed further by heating the compound to 140° with 60 cc of 85% by volume sulphuric acid for 25 minutes. The mixture is then poured into ice water, made alkaline with concentrated ammonia and the aqueous solution extracted with chloroform. After drying of the chloroform extract over potassium carbonate the solvent is evaporated and the crystalline residue recrystallised from ethanol after treatment with animal charcoal. 3-methyl-9 - [1^1 - methyl - piperidylidene - (4^1)] - 4-aza - thiaxanthene crystallises, needles as fine as hair, having a melting point of 195—196°

After crystallisation from ethanol the monohydrochloride melts at 300—303° with decomposition.

The production of the starting material, 3-methyl - 4 - aza - thiaxanthone, is described in Example 3.

EXAMPLE 5

a) 1,3 - dimethyl - 9 - (3^1 - dimethylaminopropyl) - 4 - aza - thiaxanthydrol.

In a manner analogous to that described in Example 3 the Grignard compound is produced from 5 g of a copper - magnesium alloy and 22.5 g of dimethylaminopropyl chloride in 40 cc of ether and 20 cc of tetrahydrofuran. A total of 10 g of 1,3 - dimethyl-4 - aza - thiaxanthone (melting point 147—148°) are added to the reaction mixture which has been cooled to 40° and the mixture heated at reflux for one hour. The cooled solution is then poured into 500 cc of a 10% ammonium chloride solution. The undissolved metal residues are filtered off and the solution extracted with chloroform. After drying of the chloroform extracts over potassium carbonate the solution is evaporated and the residue recrystallised from acetone. The 1,3 - dimethyl - 9-(3^1 - dimethylaminopropyl) - 4 - aza - thiaxanthydrol melts at 121—122.5°.

b) 1,3 - dimethyl - 9 - (3^1 - dimethylaminopropylidene) - 4 - aza - thiaxanthene.

11.8 g of 1,3 - dimethyl - 9 - (3^1-dimethylaminopropyl) - 4 - aza - thiaxanthydrol are heated at reflux for one hour with 100 cc of concentrated hydrochloric acid. The solution is then evaporated in a vacuum, the residue dissolved in water, the mixture made alkaline with potassium hydroxide and shaken three times with ether. After drying of the combined ether extracts over potassium carbonate and evaporation of the solvent, the residue is dissolved in methanol, the solution brought to a pH value of 5.5 with hydrobromic acid and evaporated to dryness in a vacuum. The residue is boiled with 25 cc of ethanol, the *isomer A* of 1,3 - dimethyl - 9 - (3^1 - dimethylaminopropylidene) - 4 - aza - thiaxanthene hydrobromide crystallising. After recrystallisation from ethanol it melts at 240—243° (decomposition).

The *isomer B* is obtained as follows:— Upon considerable concentration of the ethanolic mother liquor a mixture of the isomers A and B crystallises first. The mixture is filtered and ether added to the filtrate, the isomer B of 1,3 - dimethyl - 9 - (3^1 - dimethylaminopropylidene) - 4 - aza - thiaxanthene hydrobromide crystallising. It is recrystallised from acetone and then from ethanol/ether. Melting point 208—212° (decomp.).

The 1,3 - dimethyl - 4 - aza - thiaxanthone used as a starting material is produced in the following manner:—

a) 59 g of 2,4 - dimethyl - 5 - cyano - 6 - chloropyridine and 43.5 g of dry sodium thiophenolate are heated at reflux in 300 cc of dioxane for 15 hours. The resulting precipitate is filtered off and the filtrate evaporated in a vacuum. The evaporation residue is then taken up in methylene chloride, the solution washed with water, dried over magnesium sulphate and evaporated. The residue is recrystallised from methanol, the 2,4 - dimethyl - 5 - cyano-6 - phenylmercapto - pyridine having a melting point of 90—91° resulting.

b) 54 g of 2,4 - dimethyl - 5 - cyano - 6 - phenylmercaptopyridine are heated to 140° with 550 cc of concentrated sulphuric acid/water (volume 1:1) for 15 hours. A solution of 28 g of sodium nitrite in 28 cc of water is then added dropwise during the course of 30 minutes at 5°, the mixture brought to room temperature and then heated for one hour to 55° and then kept at this temperature for a further two hours. The cooled solution is then diluted with 2000 cc of ice water and brought to a pH value of 4 with ammonia. The precipitated 2,4 - dimethyl - 5 - carboxy - 6 - phenylmercapto - pyridine is filtered and recrystallised from methanol. Melting point 193—195°.

c) 52 g of 2,4 - dimethyl - 5 - carboxy - 6-phenylmercapto - pyridine are heated with 250 g of polyphosphoric acid for one hour to 120° and then to 150° for 15 minutes. The mixture is subsequently stirred into 2000 cc of water. After cooling the precipitated substance is filtered off, suspended in dilute sodium hydroxide, again filtered and dried. After crystallisation from ethanol 1,3 - dimethyl - 4 - aza - thiaxanthone melts at 147—148°.

EXAMPLE 6

a) 1,3 - dimethyl - 9 - [1^1 - methyl - piperidyl-(4^1)] - 4 - aza - thiaxanthydrol

A total of 8 g of 1,3 - dimethyl - 4 - aza-thiaxanthone (melting point 147—148°) is added portionwise at 40° to a Grignard solution obtained from 3 g of copper-magnesium alloy and 15 g of 1 - methyl - 4 - chloro - piperidine in 35 cc of tetrahydrofuran (production see Example 2), and the mixture then heated at reflux for one hour. The cooled solution is then poured into 300 cc of a 10% ammonium chloride solution. The undissolved metal residues are filtered off and the filtrate shaken with chloroform. After drying of the chloroform extracts over magnesium sulphate the solvent is evaporated and the crude 1,3 - dimethyl - 9 - [1^1 - methyl - piperidyl - (4^1)]-4 - aza - thiaxanthydrol crystallised from acetone. The pure compound melts at 204—206°

(b) 1,3 - dimethyl - 9 - [1^1 - methyl - piperidylidene - (4^1)] - 4 - aza - thiaxanthene

6 g of 1,3 - dimethyl - 9 - [1^1 - methyl-piperidyl - (4^1)] - 4 - aza - thiaxanthydrol

are heated to 140° with a mixture of 12 cc of water and 36 cc of concentrated sulphuric acid for 45 minutes. The mixture is subsequently poured into ice water, made alkaline with ammonia and the precipitated 1,3 - dimethyl - 9 - [1¹ - methyl - piperidylidene-(4¹)] - 4 - aza - thiaxanthene filtered off. The compound is dried and recrystallised from ethanol. Melting point 212—213°.

After crystallisation from ethanol/ether or isopropanol the monohydrochloride melts at 287—289° (decomposition).

The production of the 1,3 - dimethyl - 4-aza - thiaxanthone used as a starting material is described in Example 5.

EXAMPLE 7

a) 9 - (3¹ - piperidino - propyl) - 4 - aza-thiaxanthydrol

1.82 g of magnesium shavings activated with iodine are covered with a layer of 5 cc of tetrahydrofuran and 0.2 cc of ethylene bromide are added. Upon commencement of the reaction, a solution of 13.0 g of γ - chloropropyl - piperidine in 20 cc of tetrahydrofuran are added dropwise and the mixture heated for 2 hours at reflux. A total of 10.65 g of 4 - aza - thiaxanthone (melting point 234°) are added portionwise to the reaction mixture cooled to 30—40° and then 15 cc of tetrahydrofuran are added. To complete the reaction the mixture is heated at reflux for a further hour. The cooled reaction mixture is then stirred into 150 cc of a 10% ammonium chloride solution and shaken with methylene chloride. After drying of the methylene chloride extract over potassium carbonate the solvent is evaporated and the residue, 9 - (3¹ - piperidino-propyl)-4 - aza - thiaxanthydrol, recrystallised from acetone. Melting point 142—144°.

b) 9 - (3¹ - piperidino - propylidene) - 4 - aza-thiaxanthene

10 g of the resulting compound are heated at reflux together with 100 cc of concentrated hydrochloric acid for one hour. The reaction mixture is then evaporated in a vacuum, the residue dissolved in water, the aqueous solution made alkaline with potassium hydroxide and shaken with ether. After drying of the ether extract over potassium carbonate and evaporation of the solvent the remaining oil is dissolved in ethanol and the calculated quantity of hydrochloric acid for the conversion to the monohydrochloride added. The mixture is then evaporated in a vacuum and the residue dissolved in hot acetone, the 9 - (3¹ - piperidino - propylidene) - 4 - aza - thiaxanthene hydrochloride crystallising upon cooling of the solution. Melting point 219—221° (decomposition) from isopropanol.

EXAMPLE 8

a) 9 - (3¹ - pyrrolidino - propyl) - 4 - aza-thiaxanthydrol

The desired product is obtained from γ-chloropropyl - pyrrolidine and 4 - aza - thiaxanthone by a Grignard reaction and subsequent hydrolysis in a manner analogous to that described in Example 7, a).

Melting point 113—115° after recrystallisation from acetone.

b) 9 - (3¹ - pyrrolidino - propylidene) - 4-aza - thiaxanthene

9 - (3¹ - pyrrolidino - propyl) - 4 - aza-thiaxanthydrol is heated with concentrated hydrochloric acid in a manner analogous to that described in Example 7, b).

After recrystallisation from isopropanol the 9 - (3¹ - pyrrolidino - propylidene) - 4 - aza-thiaxanthene hydrochloride melts at 228° (decomposition).

EXAMPLE 9

a) 9 - [3¹ - (4¹¹ - methyl - piperazino) - propyl] - 4 - aza - thiaxanthydrol

The 9 - [3¹ - (4¹¹ - methyl - piperazino)-propyl] - 4 - aza - thiaxanthydrol is obtained as a brown oil from 1 - (γ - chloropropyl)-4 - methyl - piperazine and 4 - aza - thiaxanthone by a Grignard reaction and subsequent hydrolysis in a manner analogous to that described in Example 7, a). For the purpose of purification a solution of this oil in methylene choride is filtered through a column of aluminium oxide, some resin being removed thereby. The resulting light brown viscous base is then dissolved in ethanol and an ethanolic solution of the calculated quantity of fumaric acid added to the solution, the acid fumarate of 9 - [3¹ - (4¹¹ - methyl - piperazino) - propyl] - 4 - aza - thiaxanthydrol crystallising immediately. After crystallisation from ethanol it melts at 178—180° (decomposition).

b) 9 - [3¹ - (4¹¹ - methyl - piperazino) - propylidene] - 4 - aza - thiaxanthene

15 g of the resulting acid fumarate are heated at reflux for one hour with 100 cc of glacial acetic acid and 100 cc of concentrated hydrochloric acid in a manner analogous to that described in Example 7, b).

The dihydrochloride melts at 244—247° (decomposition) after recrystallisation from 95% by volume ethanol.

EXAMPLE 10

a) 9 - (3¹ - morpholino - propyl) - 4 - aza-thiaxanthydrol

In a manner analogous to that described in Example 7, a) the desired compound is obtained from γ - chloropropyl - morpholine and 4 - aza - thiaxanthone by a Grignard reaction and subsequent hydrolysis. Melting point 141—142° after recrystallisation from acetone.

b) 9 - (3¹ - morpholino - propylidene) - 4-aza - thiaxanthene

9 - (3¹ - morpholino - propyl) - 4 - aza-thiaxanthydrol is heated with concentrated hydrochloric acid in a manner analogous to that described in Example 7, b).

The *cis - trans* isomer mixture of 9 - (3¹-morpholino - propylidene) - 4 - aza - thiaxanthene hydrochloride melts at approximately 160—180° (decomposition) after recrystallisation from ethanol.

EXAMPLE 11

a) 9 - {[1¹ - methyl - piperidyl - (3¹)]-methyl} - 4 - aza - thiaxanthydrol

2.43 g of magnesium shavings activated with iodine are covered with a layer of 5 cc of tetrahydrofuran and 0.3 cc of ethylene bromide are added. Upon commencement of the reaction a solution of 16.2 g of 1 - methyl-piperidyl - (3) - methyl chloride in 30 cc of absolute tetrahydrofuran are added dropwise and the mixture heated at reflux until the magnesium has dissolved (1 to 2 hours). The mixture is then cooled, 10.65 g of 4 - aza-thiaxanthone added at 10—20° and the mixture stirred for a further 20 minutes at room temperature. The mixture is then stirred into 300 cc of a 10% ammonium chloride solution, shaken with methylene chloride, the extract dried over potassium carbonate and evaporated. The residue, 9 - {[1¹ - methyl - piperidyl - (3¹)] - methyl} - 4 - aza - thiaxanthydrol, is recrystallised from ethanol. Melting point 201—202°

b) 9 - {[1¹ - methyl - piperidyl - (3¹)]-methylene} - 4 - aza - thiaxanthene

40 cc of concentrated hydrochloric acid are added to a solution of 10 g of 9 - {[1¹ - methyl - piperidyl - (3¹)] - methyl} - 4-aza - thiaxanthydrol in 100 cc of glacial acetic acid and the mixture heated at reflux for one hour. The mixture is subsequently evaporated in a vacuum, the residue dissolved in water, the solution made alkaline and shaken with ether. After drying of the ethereal extract over potassium carbonate and evaporation of the solvent the residue is dissolved in ethanol and the calculated quantity of fumaric acid added to the solution. The mixture is heated for a short time until the fumaric acid has dissolved and then cooled, the neutral fumarate (*cis - trans* isomer mixture) crystallising. Melting point 231—232° (decomposition) after recrystallisation from methanol.

EXAMPLE 12

a) 9 - {[1¹ - methyl - pyrrolidyl - (3¹)]-methyl} - 4 - aza - thiaxanthydrol

The desired compound is obtained from 1-methyl - pyrrolidyl - (3) - methyl chloride and 4 - aza - thiaxanthone in a manner analogous to that described in Example 11, a). Melting point 177—178° after recrystallisation from isopropanol/petroleum ether (2:1).

b) 9 - {[1¹ - methyl - pyrrolidyl - (3¹)]-methylene} - 4 - aza - thiaxanthene

The desired compound is obtained from 9 - {[1¹ - methyl - pyrrolidyl - (3¹)]-methyl} - 4 - aza - thiaxanthydrol in a manner analogous to that described in Example 11, b). After crystallisation from methanol/15% water the *cis- trans* isomer mixture of the acid oxalate melts at 217—219° (decomposition).

EXAMPLE 13

a) 9 - {[1¹ - methyl - piperidyl - (2¹)]-ethyl} - 4 - aza - thiaxanthydrol

The desired compound is obtained from 1-methyl - piperidyl - (2) - ethyl chloride and 4 - aza - thiaxanthone, in a manner analogous to that described in Example 11, a). The compound is a viscous oil and is processed further without further purification.

b) 9 - {[1¹ - methyl - piperidyl - (2¹)]-ethylidene} - 4 - aza - thiaxanthene

The desired compound is obtained from 9-{[1¹ - methyl - piperidyl - (2¹)] - ethyl} - 4 - aza - thiaxanthydrol in a manner analogous to that described in Example 11, b). The crude isomer mixture is then dissolved in methanol and a quantity of hydrobromic acid, calculated for the monohydrobromide, added. The mixture is then evaporated in a vacuum and the residue crystallised from methanol, the *hydrobromide of isomer A* crystallising. After recrystallising twice from methanol it melts at 227—229°.

The mother liquors are allowed to crystallise and after recrystallisation from ethanol, a mixture is obtained enriched in the *hydrobromide of isomer B*. This is shaken with dilute sodium hydroxide and methylene chloride and the methylene chloride solution evaporated after drying over potassium carbonate. The residue is dissolved in ethanol and a quantity of fumaric acid, calculated for the neutral fumarate, added, the neutral fumarate crystallising after the addition of ether. After recrystallising a number of times from 95% ethanol/ether (1:1) the pure *neutral fumarate of isomer B* is obtained. Melting point 161—164° (decomposition).

EXAMPLE 14

a) 9 - {[1¹ - methyl - pyrrolidyl - (2¹)]-ethyl} - 4 - aza - thiaxanthydrol

The desired compound is obtained from 1 - methyl - pyrrolidyl - (2) - ethyl chloride and 4 - aza - thiaxanthone in a manner analogous to that described in Example 11, a). Melting point 140—142° after recrystallisation from acetone.

b) 9 - {[1¹ - methyl - pyrrolidyl - (2¹)]-ethylidene} - 4 - aza - thiaxanthene

The desired compound is obtained from 9-{[1¹ - methyl - pyrrolidyl - (2¹)] - ethyl}-4 - aza - thiaxanthydrol in a manner analogous to that described in Example 11, b). The crude isomer mixture is then dissolved in methanol and a quantity of hydrobromic acid, calculated for the monohydrobromide, added. The mixture is then evaporated in a vacuum and the residue recrystallised from methanol, the pure *monohydrobromide of isomer B* being obtained after recrystallising three times. Melting point 205—206°.

The mother liquors are evaporated. The residue is dissolved in water, the solution made alkaline and the separated bases taken up in methylene chloride. The residue remaining after drying over potassium carbonate and evaporation of the solvent is dissolved in methanol and a quantity of fumaric acid, calculated for the neutral fumarate, added to the solution, the *neutral fumarate of isomer A* crystallising. After recrystallising a number of times from methanol it melts at 196—197°.

EXAMPLE 15

a) 9 - (2¹ - methyl - 3¹ - piperidino - propyl)-4 - aza - thiaxanthydrol

The desired compound is obtained from 2-methyl - 3 - piperidino - propyl chloride and 4 - aza - thiaxanthone in a manner analogous to that described in Example 11, a). The compound is a viscous oil which is worked up further without further purification.

b) 9 - (2¹ - methyl - 3¹ - piperidino - propylidene) - 4 - aza - thiaxanthene

The desired compound is obtained from 9-(2¹ - methyl - 3¹ - piperidino - propyl) - 4 - aza - thiaxanthydrol in a manner analogous to that described in Example 11, b). The crude product is first of all distilled in a bulb tube, a yellow, viscous oil distilling over at 0.05 mm of Hg from 200—220° (bath temperature). It is dissolved in methanol, the quantity of hydrochloric acid calculated for the monohydrochloride added, the mixture evaporated in a vacuum and the residue crystallised from ethanol/ether. The crystals are recrystallised twice from ethanol. The *monohydrochloride of isomer A* melts at 235—237°.

The mother liquors are evaporated. The residue is dissolved in water, the solution made alkaline and the precipitated substance taken up in methylene chloride. The residue remaining after drying over potassium carbonate and evaporation of the solvent is dissolved in ethanol, the *isomer B* of 9 - (2¹ - methyl - 3¹-piperidino - propylidene) - 4 - aza - thiaxanthene crystallising upon cooling of this solution. Melting point after recrystallising twice from ethanol 122—124°. After crystallisation from ethanol/ether the *hydrochloride of the isomer B* produced therefrom melts at 207—208°.

EXAMPLE 16

a) 9 - (3¹ - dimethylamino - *n* - butyl - 4 - aza - thiaxanthydrol

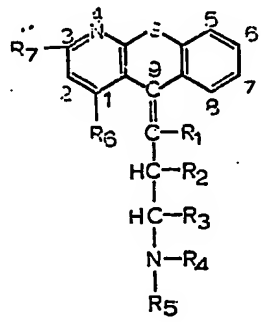
The desired compound is obtained from 3-dimethylamino - butyl chloride and 4 - aza-thiaxanthone in a manner analogous to that described in Example 11, a). After recrystallisation from acetone it has a melting range of 145—158°.

b) 9 - (3¹ - dimethylamino - butylidene) - 4-aza - thiaxanthene

The desired compound is obtained from 9-(3¹ - dimethylamino - *n* - butyl) - 4 - aza-thiaxanthydrol in a manner analogous to that described in Example 11, b). The *cis- trans* isomer mixture of the neutral fumarates melts at 185—192° after crystallisation from methanol.

WHAT WE CLAIM IS:—

1. A process for the production of compounds of general formula I,



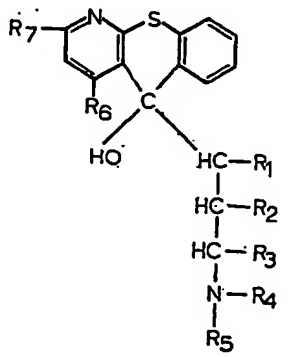
I

in which R_1 signifies a hydrogen atom,

each of R_2, R_3, R_6 and R_7 signifies a hydrogen atom or a methyl or ethyl radical and

each of R_4 and R_5 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive or R_4 and R_5 together signify an alkylene radical containing 4 or 5 carbon atoms, which alkylene radical may have interposed an oxygen atom or a nitrogen atom substituted with an alkyl radical containing from 1 to 4 carbon atoms inclusive, with the proviso that, when R_5 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive, two of the symbols R_1, R_2 and R_3 may each signify a hydrogen atom and the third together with R_4 a straight chain alkylene radical containing from 2 to 4 carbon atoms inclusive, and with the further proviso that when the 9-substituent is heterocyclic the ring of which it consists or which forms part of it must be a 5 or 6 membered one, and their acid addition salts, characterised in that water is split off from a

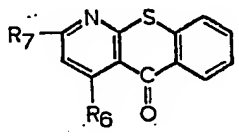
9 - hydroxy - 4 - aza - thiaxanthene derivative of general formula IV,



IV

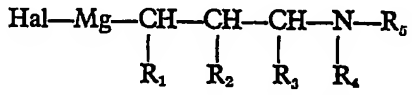
in which R_1 to R_7 have the above significance, and, when an acid addition salt is desired, salification is effected with an organic or inorganic acid.

2. A process according to Claim 1, characterised in that the compound IV is produced by hydrolysing a complex formed by condensing a 4 - aza - thiaxanthone of general formula II,



II

in which R_6 and R_7 have the significance stated in Claim 1, with an organometallic compound of general formula III,



III

in which R_1 to R_5 have the significance stated in Claim 1 and Hal signifies a chlorine, bromine or iodine atom.

3. A process for the production of compounds of general formula I stated in Claim 1 and their acid addition salts, substantially as herein described with reference to any one of the Examples.

4. Compounds of general formula I stated in Claim 1, and their acid addition salts, whenever produced by a process as claimed in any one of the preceding Claims.

5. The compounds of general formula I stated in Claim 1 and their acid addition salts.

6. 9 - (3^1 - dimethylamino - propylidene) - 4 - aza - thiaxanthene.

7. 9 - [1^1 - methyl - piperidylidene - (4^1)] - 4 - aza - thiaxanthene.

8. 3 - methyl - 9 - (3^1 - dimethylamino-propylidene) - 4 - aza - thiaxanthene.

9. 3 - methyl - 9 - [1^1 - methyl - piperidylidene - (4^1)] - 4 - aza - thiaxanthene.

10. 1,3 - dimethyl - 9 - (3^1 - dimethylamino - propylidene) - 4 - aza - thiaxanthene.

11. 1,3 - dimethyl - 9 - [1^1 - methyl-piperidylidene - (4^1)] - 4 - aza - thiaxanthene.

12. 9 - (3^1 - piperidino - propylidene) - 4 - aza - thiaxanthene.

13. 9 - (3^1 - pyrrolidino - propylidene) - 4-aza - thiaxanthene.

14. 9 - [3^1 - (4^{11} - methyl - piperazino)-propylidene] - 4 - aza - thiaxanthene.

15. 9 - (3^1 - morpholino - propylidene) - 4-aza - thiaxanthene.

16. 9 - {[1^1 - methyl - piperidyl - (3^1)]-methylene} - 4 - aza - thiaxanthene.

17. 9 - {[1^1 - methyl - pyrrolidyl - (3^1)]-methylene} - 4 - aza - thiaxanthene.

18. 9 - {[1^1 - methyl - piperidyl - (2^1)]-ethylidene} - 4 - aza - thiaxanthene.

19. 9 - {[1^1 - methyl - pyrrolidyl - (2^1)]-ethylidene} - 4 - aza - thiaxanthene.

20. 9 - (2^1 - methyl - 3^1 - piperidino - propylidene) - 4 - aza - thiaxanthene.

21. 9 - (3^1 - dimethylamino - butylidene)-4 - aza - thiaxanthene.

22. The acid addition salts of the compounds claimed in any one of Claims 6 to 21.

23. Pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, a compound claimed in any one of Claims 4 to 22.

G. H. MUNSTER & CO.,
Chartered Patent Agents,
Imperial Buildings, 56, Kingsway, London,
W.C.2.

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